

BJR



## ■ INFECTION

# Underestimation of *Staphylococcus aureus* (MRSA and MSSA) carriage associated with standard culturing techniques

ONE THIRD OF CARRIERS MISSED

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## Objectives

Nasal carriers of *Staphylococcus (S.) aureus* (MRSA and MSSA) have an increased risk for healthcare-associated infections. There are currently limited national screening policies for the detection of *S. aureus* despite the World Health Organization's recommendations. This study aimed to evaluate the diagnostic performance of molecular and culture techniques in *S. aureus* screening, determine the cause of any discrepancy between the diagnostic techniques, and model the potential effect of different diagnostic techniques on *S. aureus* detection in orthopaedic patients.

## Methods

Paired nasal swabs for polymerase chain reaction (PCR) assay and culture of *S. aureus* were collected from a study population of 273 orthopaedic outpatients due to undergo joint arthroplasty surgery.

## Results

The prevalence of MSSA nasal colonization was found to be between 22.4% to 35.6%. The current standard direct culturing methods for detecting *S. aureus* significantly underestimated the prevalence ( $p=0.005$ ), failing to identify its presence in approximately one-third of patients undergoing joint arthroplasty surgery.

## Conclusion

Modelling these results to national surveillance data, it was estimated that approximately 5000 to 8000 *S. aureus* surgical site infections could be prevented, and approximately \$140million to \$950million (approximately £110million to £760million) saved in treatment costs annually in the United States and United Kingdom combined, by using alternative diagnostic methods to direct culture in preoperative *S. aureus* screening and eradication programmes.

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## Article focus

■ This study aimed to evaluate the diagnostic performance of molecular and culture techniques in *S. aureus* screening, determine the cause of any discrepancy between the diagnostic techniques; and model the potential effect of different diagnostic techniques on *S. aureus* detection in orthopaedic patients.

## Key messages

■ The prevalence of MSSA nasal colonization was found to be between 22.4% and 35.6%.

- Polymerase chain reaction or preplating broth enrichment of swabs for culture can significantly improve nasal MSSA detection.
- Use of optimal techniques could prevent up to 8000 MSSA SSIs per annum in the United States and United Kingdom combined.

## Strengths and limitations

- This study provides the first evaluation of the effect that different diagnostic methods have on the prevalence of nasal MSSA colonization in an elective orthopaedic population.

- The main limitation of this study was that PCR-negative samples were not analyzed in the cohort of samples undergoing enrichment, preventing a complete evaluation of the enrichment technique.

## Introduction

Healthcare-associated infection is a significant clinical issue, particularly surgical site infection (SSI). SSI is widely used as a quality indicator in healthcare systems and reporting is mandatory in many settings, notably by Surgical Site Infection Surveillance Service (SSISS) from Public Health England<sup>1</sup> and through the Center for Disease Control (CDC) in the United States.<sup>2</sup> Orthopaedic surgery is a primary focus of SSI surveillance, given the very high rates of implant surgery and the major impact that SSI can have on patients' health-related quality of life, function, healthcare costs, and medicolegal implications.<sup>3</sup>

The reported SSI incidence for knee and hip arthroplasties undertaken in developed nations has been estimated to be between 0.5% and 2%, based on inpatient, readmission episodes, and the number of revision procedures that are performed.<sup>4–8</sup> However, even national surveillance estimates may under-report the true incidence.<sup>9</sup> The available data suggests that downward trends have levelled off, although rates for knee surgery may be rising.<sup>8</sup> This could reflect a changing prevalence of risk factors for infection, such as revision surgery, longer operation times, higher BMI, and greater patient comorbidity. Gram-positive bacteria have been reported as accounting for 46% of all SSIs, in all branches of surgery. For hip and knee arthroplasty, among monomicrobial infections (which account for around 75% of all patients), between 30% and 38% were methicillin-sensitive *Staphylococcus* (*S.*) *aureus* (*MSSA*), between 4% and 5% were methicillin-resistant *S. aureus* (*MRSA*), and between 25% and 28% were coagulase negative staphylococci. In polymicrobial cases Gram-positive organisms were implicated in between 70% and 80% of patients.<sup>8</sup> For orthopaedic surgery, Gram-positive organisms account for the majority of SSIs.<sup>8</sup>

High-level nasal carriers of *MSSA* have a risk of healthcare-associated *MSSA* infection that is three to six times the risk compared with noncarriers and low-level carriers<sup>10</sup> and is similar in both surgical and non-surgical hospitalized patients.<sup>11,12</sup> It is also known that more than 80% of healthcare-associated *S. aureus* infections are endogenous, implying that acquisition is from sites on the patient's own body.<sup>13,14</sup> The association between nasal carriage of *S. aureus*, specifically *MRSA*, and SSI has been demonstrated in a systematic review and confirmed in recent cohort studies.<sup>15,16</sup>

A pan-European study reported that 21.6% of healthy European residents carry *S. aureus* in their nose, with the rate in the United Kingdom being 25%, although there was wide variation between countries.<sup>17</sup> A recent

retrospective part cohort United Kingdom-based study among patients undergoing elective orthopaedic surgery reported a threefold reduction in *MSSA*-associated SSI, using a routine preoperative screening and decolonization programme.<sup>18</sup> In contrast to *MSSA*, *MRSA* prevalence in healthy community individuals is estimated to be < 2%.<sup>19</sup> Screening of patients presenting for surgery or admitted to hospital areas with strong risk factors for *MRSA*, such as intensive care units (ICUs), dialysis units, and elderly care areas, is widely practised in healthcare systems. The National Screening policy for *MRSA*<sup>20</sup> in the United Kingdom recommends the use of two swabs (a nasal swab plus a perineal or throat swab) cultured directly or following pre-enrichment onto chromogenic *MRSA*-selective media. As primary screening media, the American Society for Microbiology recommends salt-containing tryptone soya broth (TSB) in conjunction with a blood agar plate and mannitol-salt agar (MSA) containing 4 µg of oxacillin per millilitre.<sup>21</sup> There are currently no national screening policies for *MSSA* in the United Kingdom or United States prior to orthopaedic surgery, despite the recent recommendations from the World Health Organization.<sup>22</sup>

The aims of this study were to evaluate the diagnostic performance of molecular and culture techniques in *S. aureus* screening using paired nasal samples, to determine the cause of any discrepancy between the diagnostic techniques and to model the potential effect of different diagnostic techniques on *S. aureus* detection in orthopaedic patients.

## Materials and Methods

Nasal swabs for polymerase chain reaction (PCR) assay and culture of *S. aureus* were collected from a study population of 273 orthopaedic outpatients due to undergo joint arthroplasty surgery at a university teaching hospital (Royal Infirmary Edinburgh) between October 2015 and September 2016. The study protocol was reviewed and approved by the regional ethics committee (REC 15/SS/0091). Patients presenting for assessment prior to orthopaedic implant surgery were prospectively enrolled and provided written consent. All specimens were collected by trained research nurses and were processed within three hours of collection. Patient data was anonymized, processed, and stored in accordance with established guidelines.<sup>23</sup>

The Xpert *S. aureus* Nasal Complete Assay (Cepheid, Sunnyvale, California) was carried out according to the manufacturer's instructions. Swab tips (Sample Collection device, Cepheid) were placed in elution buffer, vortexed, and added to a test cartridge, which was loaded into the GeneXpert (Cepheid) Instrument. Primers and probes are included to detect *S. aureus* (staphylococcal protein A, *spa*) as well as two markers of methicillin resistance (the methicillin resistance gene *mecA* and the staphylococcal

**Table I.** Complete results of Xpert PCR assay, direct culture, and pre-enrichment culture for *Staphylococcus aureus* nasal screening

Assay	Positive, n (%)			Negative, n (%)	Result not available
	MSSA	MRSA	Total		
Xpert PCR assay (n=273)	94 (35.6)	6 (2.3)	100 (37.9)	164 (62.1)	9*
Direct culture (n=181)	37 (22.4)	2 (1.2)	39 (23.6)	126 (76.4)	16†
Pre-enrichment culture (n=92)	28 (80.0)	3 (8.6)	31 (88.6)	4 (11.4)	57‡

\*Invalid result by Xpert PCR

†Culture not performed in line with study protocol

‡Enrichment not performed on Xpert PCR negative samples

MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction

cassette chromosome (SCCmec)). Standard swabs (Amies Transport Swab, Sarstedt, Nümbrecht, Germany) were plated directly to solid agar while enrichment swabs (Sigma Tryptic Soy broth with 6.5% NaCl, (Medical Wire & Equipment, Corsham, Wiltshire, United Kingdom)) were incubated for between 18 and 24 hours at 37°C prior to plating. To aid detection of both MRSA and MSSA, swabs were subbed to *Brilliance MRSA 2* Agar (Thermo Fisher Scientific Oxoid, Basingstoke, Hampshire, United Kingdom) and mannitol salt agar (MSA) (Thermo Fisher Scientific Oxoid). Culture plates were incubated for between 18 and 24 hours at 37°C. After incubation, presumptive *S. aureus* colonies (denim blue on chromogenic agar or yellow on MSA) were subcultured to Columbia blood agar (CBA) (Thermo Fisher Scientific Oxoid, Basingstoke, Hampshire, UK) for identification using a MicroFlex MALDI-TOF mass spectrometer (Bruker Daltonics, Billerica, Massachusetts). For isolates confirmed as *S. aureus*, antibiotic sensitivity testing was performed on the VITEK 2 system (bioMérieux, Marcy-l'Étoile, France) using AST P-634 cards. A further PCR assay was conducted in 58 randomly selected samples as part of a discrepant analysis. After processing for culture, swabs were held at 4°C for up to seven days before storing at -80°C. Swabs were placed in Microtest M4-RT transport medium (Remel, San Diego, California), vortexed for ten seconds, and 200 µl of the liquid was stored. Samples were thawed and nucleic acid was extracted as previously described.<sup>24</sup> After thawing, the samples were processed using a standard protocol for real-time PCR detection of *S. aureus* thermostable nuclease (*nuc*) gene using the ABI 7500 Fast Instrument (Applied Biosystems, Foster City, California).<sup>25</sup>

Data were analyzed using SPSS statistical software version 22.0 (IBM Inc., Armonk, New York) and Minitab version 17.1.0 (Minitab Ltd, Coventry, Warwickshire, United Kingdom). Fisher's exact test was used to compare the diagnostic performance of each technique. A discrepant analysis was performed to determine the cause of any difference between the estimated prevalence.<sup>26</sup> Using the results of both PCR assays as the benchmark the performance characteristics were calculated. Sensitivity analysis was conducted using 95% confidence intervals (CIs) generated from the paired sample data. A p-value < 0.05 was deemed to be statistically significant.

Using data reported in the literature, the risk of *S. aureus* SSI in patients with known nasal colonization, the risk reduction associated with a preoperative MSSA screening and eradication, and annual rates of joint arthroplasty surgery were estimated. These estimates were combined with the diagnostic performance characteristics from the paired nasal samples to model the effect discrepancies in diagnostic performance would have on national MSSA SSI incidence.

## Results

In the 273 patients undergoing nasal screening, the median age was 68 years (interquartile range (IQR) 61 to 75), 176 of whom were female (64.5%). Of these patients, 239 (87.6%) were due to undergo primary hip or knee arthroplasty. From the initial 273 paired samples, a total of 16 sample pairs (5.9%) were excluded due to Xpert assay failure (n=9, 3.3%) or failure to perform culture as per study protocol (n=7, 2.6%), leaving 257 paired samples available for analysis. The results of the PCR and culture assays are shown in Table I. The Xpert PCR assay found 37.9% of samples to be positive (95% confidence interval (CI) 32.0 to 44.0), with 35.6% MSSA (95% CI 29.8 to 41.7) and 2.3% MRSA (95% CI 0.8 to 4.9). Direct culture found 23.6% of samples to be positive (95% CI 17.4 to 30.9), with 22.4% (95% CI 16.3 to 29.6) and 1.2% (95% CI 0.1 to 4.3) confirmed as MSSA and MRSA, respectively. Pre-enriched culture found 33.7% of samples to be positive (95% CI 24.2 to 44.3), with 30.4% MSSA (95% CI 21.3 to 40.9) and 4.3% MRSA (95% CI 1.2 to 10.8).

A summary of the performance characteristics taken from the 58 paired samples that underwent both PCR assays and either direct or pre-enriched culture is shown in Table I. Analysis of the data suggested that the cause of the discrepancy was due to a lack of sensitivity associated with direct culture.

The absolute difference in estimated prevalence of nasal MSSA colonization between the PCR assay and direct culture was 13.1% (95% CI 4.6 to 21.8), which was statistically significant (p=0.005). Exclusive use of direct culture would estimate the MSSA prevalence 8.0% (95% CI 3.3 to 19.4) lower than pre-enriched culture, which was not statistically significant (p=0.167).

**Table II.** Potential prevention of *Staphylococcus (S.) aureus* surgical site infections in the United Kingdom and United States

	Approx. no. of PJAs per annum	No. of patients with nasal MSSA colonization potentially missed*	No. of preventable <i>S. aureus</i> SSIs†	Approx. treatment costs potentially saved‡
United States	1 000 000	80 000 to 130 000	4000 to 6600	\$120 million to \$790 million
England, Wales, and Northern Ireland	182 000	15 000 to 24 000	800 to 1200	\$20 million to \$150 million§
Scotland	16 000	1200 to 2000	60 to 100	\$1.5 million to \$12.5 million¶
Total	1 198 000	96 200 to 156 000	4860 to 7900	\$141.5 million to \$952.5 million

\*The approximate number of patients with nasal MSSA colonization who would be missed if direct culture were to be used exclusively over polymerase chain reaction or pre-enriched culture

†The number of surgical site infections that could potentially be prevented if polymerase chain reaction or pre-enriched culture were used, rather than direct culture, in *Staphylococcus aureus* screening programmes

‡The approximate amount that could be saved in treatment costs if polymerase chain reaction or pre-enriched culture were used, rather than direct culture, in *Staphylococcus aureus* screening programmes

§Converted from GBP (£16 million to £120 million) to USD at a rate of £1 = \$1.25 (the mean GBP to USD rate for February 2017, rounded to the nearest five cents)

¶Converted from GBP (£1.2 million to £10 million) to USD at a rate of £1 = \$1.25 (the mean GBP to USD rate for February 2017, rounded to the nearest five cents)

Approx., approximate; PJAs, primary joint arthroplasties; SSIs, surgical site infections; PCR, polymerase chain reaction

It is estimated that almost 1 200 000 primary joint arthroplasties are performed annually in the United States and United Kingdom combined (Table II).<sup>27-29</sup> If direct culture were to be used exclusively over PCR or pre-enriched culture in the United Kingdom and the United States, approximately 96 200 to 156 000 such patients with nasal MSSA colonization would be missed (Table II). It has previously been reported that nasal *S. aureus* colonization has an absolute risk of *S. aureus* SSI of 7.7% in elective orthopaedic patients (95% CI 5.4 to 10.8).<sup>30</sup> *S. aureus* screening and eradication programmes prior to elective orthopaedic surgery have a reported relative risk reduction of 66.4% (95% CI 45.8 to 87.0) for the prevention of *S. aureus* SSI.<sup>18,30-34</sup> According to economic estimates in the United States, the hospital treatment costs for an individual patient with prosthetic joint infection (PJI) range from \$30 000 to \$120 000.<sup>35-37</sup> Estimates in the United Kingdom for total hospital care costs per case are similar to that in the United States (between £20 000 and £100 000).<sup>38,39</sup> Therefore, 4860 to 7900 *S. aureus* SSIs could potentially be prevented, and approximately \$140 million to \$950 million (approximately £110 million to £760 million) saved in treatment costs in the United Kingdom and the United States combined, by using PCR or enrichment culture, rather than direct culture in *S. aureus* screening programmes (Table II).

## Discussion

This study provides the first evaluation of the effect that different diagnostic methods have on the prevalence of nasal MSSA colonization in a United Kingdom elective orthopaedic population. Using a combination of published data and the results of this study, the likely effect on *S. aureus* SSI incidence, if direct culture methods are adopted nationally, has been modelled.

The MSSA prevalence in this study was estimated to be between 22.4% and 35.6%, depending on the diagnostic method, broadly in line with previous studies.<sup>18,40-43</sup> Meenan et al<sup>40</sup> reported an *S. aureus* prevalence rate of 41.7% in a cohort of 204 obstetrics and gynaecology

patients in Ireland. The prevalence of MSSA and MRSA was 40.7% and 1.0%, respectively. Nadimpalli et al<sup>41</sup> found out of 210 workers exposed to livestock production facilities in the USA, 83 (40%) had nasal *S. aureus* colonization. Van Vugt et al<sup>42</sup> reported a nasal *S. aureus* colonization rate of 40.5% amongst 366 surgeons and surgical trainees, compared with a 30.8% prevalence out of 950 in a healthy non-hospitalized control group in The Netherlands. A recent United Kingdom-wide study of elective orthopaedics patients reported an MSSA prevalence of 29% using direct culturing techniques alone (89 MSSA positive patients of 307 elective patients screened).<sup>18</sup> In a review of longitudinal studies Wertheim et al<sup>43</sup> reported that “a mean of about 20% (12% to 30%) of individuals are persistent *S. aureus* nasal carriers, approximately a mean of 30% are intermittent carriers (16% to 70%) and about 50% (16% to 69%) are non-carriers”. It is likely that the *S. aureus* carriers in this study represent a mix of persistent and intermittent carriers who have been in contact with health care facilities, which may explain the higher prevalence rate.

The performance characteristics of the PCR assay and pre-enriched culture were found to be similar in this study. Both techniques were found to be more sensitive than direct culture in the detection of nasal MSSA. There was increased cost for consumables and processing of the PCR assay (£28/\$35) compared with pre-enriched culture (£14/\$18) and direct culture (£13/\$16). Previous studies have reported mixed performance characteristics when comparing PCR to culture techniques. Andriess et al<sup>44</sup> reported a lower sensitivity for two PCR assays (82.0% and 85.6%) in comparison to a pre-enriched semi-quantitative culture technique (98.2%) in the detection of MSSA nasal colonization when using pre-enriched conventional culture as a benchmark. Wassenberg et al<sup>45</sup> performed an evaluation of the GeneOhm MRSA (Becton Dickinson Diagnostics, San Diego, California) and GeneXpert MRSA PCR assays, as well as direct culture onto a selective, chromogenic agar (MRSA-ID, bioMérieux) using direct conventional culture as the reference in the



detection of MRSA in non-critical care hospital admissions. The PCR assays were found to have 85.2% and 75.0% sensitivity, and 96.5% and 94.5% specificity, respectively. Direct culture on chromogenic agar had an 85.7% and 96.6% sensitivity and specificity, respectively.<sup>45</sup> A similar study was repeated by the same group in Dutch ICU admissions, with higher sensitivity levels (100%) and similar specificity levels (95.7%) associated with the GeneXpert MRSA assay. No MRSA were detected using the culture technique in this Dutch ICU study and thus the sensitivity could not be calculated. The specificity of culture using chromogenic agar was 93.3%.<sup>46</sup> In contrast, Bebkö et al<sup>47</sup> reported a higher detection level with PCR compared with direct culture when they evaluated the diagnostic performance of the GeneXpert assay in patients prior to undergoing orthopaedic implant surgery. They reported that PCR assay had a 100% sensitivity and 77.1% specificity when used for detection of nasal MSSA, when using culture as the benchmark.

Previous comparisons between pre-enrichment and direct culture for the recovery of MSSA from clinical samples have been reported. McAllister et al<sup>48</sup> found that enrichment of swabs using TSB increased sensitivity for *S. aureus* by 13% compared with direct plating when using MSA culture medium in 600 HIV-positive outpatients. Meenan et al<sup>40</sup> reported a 16% increase in sensitivity with enrichment, using brain-heart infusion, when compared to direct plating onto CBA. In the same study, enrichment of swabs increased sensitivity for *S. aureus* by 31% compared with direct plating onto a selective chromogenic agar (bioMérieux *S. aureus* ID medium agar). In our study, enrichment increased the sensitivity for *S. aureus* by 21% compared with direct plating, a greater increase than reported by McAllister et al<sup>48</sup> in HIV positive patients. The sensitivity for the detection of nasal *S. aureus* associated with enrichment of swabs in our study was similar to that reported by Nadimpalli et al.<sup>41</sup> They found enrichment (Mueller-Hinton broth, 6.5% NaCl) of nasal swabs was associated with an 80.7% and 90.4% sensitivity for *S. aureus* when using Baird-Parker agar and a chromogenic agar, respectively. They also found reported high inter-observer agreement, kappa coefficient 0.69 (95% CI 0.59 to 0.80), between the two-culture media.<sup>41</sup> Despite the favourable performance characteristics of both PCR and enrichment culture, the barriers to universal uptake have been cost-effectiveness<sup>45,49</sup> and increased processing time,<sup>49,50</sup> respectively.

The main limitation of this study was that PCR-negative samples were not analyzed in the cohort of samples undergoing enrichment. This prevented a complete evaluation, with receiver operating characteristic analysis, of the enrichment technique. The decision not to analyze these samples was based on the high specificity (98%) demonstrated by the direct plating technique. A further limitation was that we compared culture with a test that is not a universally accepted gold standard (i.e. combined

PCR assays). PCR detects nucleic acid and does not distinguish between dead or live bacteria; as only viable bacteria are detected by culture, it is possible the sensitivities we report for culture may be falsely low. However, we believe that this is not the case as we show enrichment provides a similar sensitivity to PCR, suggesting that the false negatives with direct culture are due to missed low-level positive samples. Data were derived from the literature during the modelling process, which made it necessary to use assumptions that may affect the validity of the estimates produced.

In summary, we found the prevalence of MSSA nasal colonization was found to be between 22% and 36%. The use of PCR assays or pre-plating enrichment of swabs in TSB significantly improves nasal MSSA detection levels, which is relevant to both future research and clinical practice. These results should be considered when interpreting prevalence studies, when evaluating interventional studies, and in the development of future screening and decolonization strategies.

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#### Author Contribution

S. T. J. Tsang: Study conception and design, Collecting and analyzing the data, Writing and editing the manuscript.  
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D. Guerendian: Collecting and analyzing the data, Editing the manuscript.  
P. J. Gwynne: Analyzing the data, Writing and editing the manuscript.  
J. Boyd: Study conception and design, Collecting and analyzing the data, Writing and editing the manuscript.  
A. H. R. W. Simpson: Study conception and design, data analysis, writing and editing of manuscript.  
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#### Ethical Statement

This study was approved by the South-east Scotland Research Ethics Committee (reference 15/SS/0091) and witnessed consent was obtained from all enrolled patients.

#### Conflicts of Interest Statement

The authors declare that there are no conflicts of interest.

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